Reply to E. Hindié and K.R. Hess

Long, Georgina V ; Dummer, Reinhard ; Schadendorf, Dirk ; Santinami, Mario ; Atkinson, Victoria ; Mandalà, Mario ; Chiarion-Sileni, Vanna ; Larkin, James ; Nyakas, Marta ; Dutriaux, Caroline ; Haydon, Andrew ; Robert, Caroline ; Mortier, Laurent ; Schachter, Jacob ; Lesimple, Thierry ; Plummer, Ruth ; Dasgupta, Kohinoor ; Haas, Tomas ; Shilkrut, Mark ; Gasal, Eduard ; Kefford, Richard ; Kirkwood, John M ; Hauschild, Axel

DOI: https://doi.org/10.1200/JCO.19.00004

Reply to E. Hindié and K.R. Hess

Hindié[1] has pointed out that the absolute difference in 4-year relapse-free survival (RFS) rates between the treatment and placebo arms in patients with stage IIIA disease (7%) was considerably lower compared with rates in patients with stage IIIB disease (19%) and stage IIIC disease (16%; all American Joint Commission on Cancer [AJCC] 7th edition). However, the hazard ratio (HR) for RFS, which measures the reduction in risk regardless of absolute baseline risk, was consistent across substages. HR for stage IIIA disease (AJCC 7th edition melanoma staging system) was 0.58, which represents a 42% reduction in risk, 0.49 for stage IIIB disease (51% reduction in risk), and 0.46 for stage IIIC disease (54% reduction in risk). These data demonstrate that the magnitude of the RFS benefit of adjuvant dabrafenib and trametinib was consistent across substages and comparable to the overall treatment effect observed in the intention-to-treat population.[2] Therefore, it cannot be assumed that there would be a different risk reduction for patients with low-risk stage IIIA disease ($\leq$ 1 mm) on the basis of available data; however, a prospective study is needed to confirm these findings in patients with stage IIIA melanoma ($\leq$ 1 mm).

As Hindié[1] indicates, patients with stage IIIA melanoma in the COMBI-AD study had a nodal burden of greater than 1 mm. Therefore, similar to prespecified analyses by the AJCC 7th edition melanoma staging system, post hoc analyses by the AJCC 8th edition melanoma staging system included patients with lymph node metastasis of greater than 1 mm.

The adverse event profile in the COMBI-AD trial was consistent with the approved indications in metastatic melanoma, non–small-cell lung cancer, and anaplastic thyroid cancer. Adverse events were reversible and manageable, as indicated by a median duration of exposure that was close to the planned 12 months of treatment (11.0 months for dabrafenib plus trametinib and 10.0 months for placebo[3]). The most common adverse event reported was pyrexia, which could be managed with dose interruptions and supportive measures—for example, acetaminophen or corticosteroids.

Evaluation of treatment risks and benefits is important and must be discussed by the physician and patient before initiating adjuvant treatment, which would include a discussion of the absolute baseline risk of recurrence. The effect of relapse of melanoma at any stage can be devastating, especially in the case of systemic relapse. In the study cited by Hindié,[1] estimated 5-year survival rates after first relapse were similar in patients with stage IIIA and IIIB disease (20%). Of note, the type of metastasis—in-transit or nodal versus systemic—but not melanoma substage was independently associated with overall survival after first relapse.[4] Therefore, it is important to discuss adjuvant treatment options with patients with stage IIIA melanoma (lymph node metastasis $>$ 1 mm).

In reply to Hess,[5] our article presents updated efficacy results with 10 months of additional follow up that confirms RFS benefit with adjuvant dabrafenib plus trametinib. The benefit is clearly demonstrated with the more mature RFS analysis and the cure rate model.

Departure from the proportional hazards assumption discussed in the letter by Hess[5] is not unexpected in the adjuvant setting in which RFS Kaplan-Meier curves begin to plateau at a certain point in time, indicating the presence of a fraction of patients who will likely never experience disease recurrence and may be cured. In the COMBI-AD trial, RFS curves become more or less parallel beyond 3 years and the difference between curve tails is quantified by the cure rate model estimates. We agree with Hess[5] that, in this setting, RFS HR alone (HR, 0.49) may not show the entire picture regarding the efficacy of the tested drug versus control, and this is precisely the rationale for complementing the RFS HR with cure rate estimates (54% *v* 37%), as we did in this analysis.

Georgina V. Long, MD, PhD
Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, NSW, Australia

Reinhard Dummer, MD
University Hospital Zürich Skin Cancer Center, Zürich, Switzerland

Dirk Schadendorf, MD, PhD
University Hospital Essen, Essen, Germany, and German Cancer Consortium, Heidelberg, Germany

Mario Santinami, MD
Fondazione Istituto Nazionale Tumori, Milan, Italy

Victoria Atkinson, MD
Princess Alexandra Hospital, Gallipoli Medical Research Foundation, and University of Queensland, Brisbane, QLD, Australia

Mario Mandalà, MD
Papa Giovanni XXIII Cancer Center Hospital, Bergamo, Italy

Vanna Chiarion-Sileni, MD
Veneto Institute of Oncology–Istituto di Ricovero e Cura a Carattere Scientifico, Padua, Italy

James Larkin, MD, PhD
Royal Marsden National Health Service Foundation Trust, London, United Kingdom

Marta Nyakas, MD
Oslo University Hospital, Oslo, Norway

Caroline Dutriaux, MD
Centre Hospitalier Universitaire de Bordeaux, Hôpital Saint-André, Bordeaux, France

Andrew Haydon, MD, PhD
The Alfred Hospital, Melbourne, VIC, Australia

Caroline Robert, MD, PhD
Institute Gustave Roussy, Paris, France

Laurent Mortier, MD, PhD
Université de Lille, Institut National de la Santé et de la Recherche Médicale U 1189, Centre Hospitalier Universitaire Lille, Lille, France

Jacob Schachter, MD, PhD
Sheba Medical Center, Tel HaShomer, Israel, and Tel Aviv University, Tel Aviv, Israel

Thierry Lesimple, MD, MSc
Centre Eugène Marquis, Rennes, France

Ruth Plummer, MD, PhD
Freeman Hospital and Newcastle University, Newcastle upon Tyne, United Kingdom

Kohinoor Dasgupta, PhD
Novartis Healthcare, Hyderabad, India

Tomas Haas, PhD
Novartis AG, Basel, Switzerland

Mark Shilkrut, MD, PhD and Eduard Gasal, MD
Novartis Pharmaceuticals, East Hanover, NJ

Richard Kefford, MD, PhD
Melanoma Institute Australia, The University of Sydney, Macquarie University, and Westmead Hospital, Sydney, NSW, Australia

John M. Kirkwood, MD
UPMC Hillman Cancer Center, University of Pittsburgh, Pittsburgh, PA

Axel Hauschild, MD
University Hospital Schleswig-Holstein, Kiel, Germany

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.00004.

ACKNOWLEDGMENT

COMBI-AD was originally sponsored by GlaxoSmithKline; dabrafenib and trametinib were designated as assets of Novartis on March 2, 2015, after which Novartis took over sponsorship of the trial. Novartis funded editorial assistance provided by Michael Demars, PhD (Articulate Science, LLC).

REFERENCES

1. Hindié E: What is the role of dabrafenib plus trametinib adjuvant therapy in stage IIIA melanoma? J Clin Oncol 37:1355-1356, 2018
2. Hauschild A, Dummer R, Schadendorf D, et al: Longer follow-up confirms relapse-free survival benefit with adjuvant dabrafenib plus trametinib in patients with resected *BRAF* V600–mutant stage III melanoma. J Clin Oncol 36:3441-3449, 2018
3. Long GV, Hauschild A, Santinami M, et al: Adjuvant debrafenib plus trametinib in stage III BRAF-mutated melanoma. N Engl J Med 377: 1813-1823, 2017
4. Romano E, Scordo M, Dusza SW, et al: Site and timing of first relapse in stage III melanoma patients: Implications for follow-up guidelines. J Clin Oncol 28: 3042-3047, 2010
5. Hess KR: Beneficial effect of adjuvant dabrafenib plus trametinib on recurrence-frees Survival in patients with resected BRAFV600-mutant stage III melanoma seems to be short-lived. J Clin Oncol 37:1354-1355, 2018

DOI: https://doi.org/10.1200/JCO.19.00004; Published at jco.org on April 2, 2019.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Reply to E. Hindié and K.R. Hess

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Georgina V. Long
Honoraria: Bristol-Myers Squibb, Merck, Roche, Novartis, Incyte
Consulting or Advisory Role: Bristol-Myers Squibb, Roche/Genentech, Amgen, Merck, Novartis, Array BioPharma, Pierre Fabre

Reinhard Dummer
Honoraria: Roche, Novartis, Bristol-Myers Squibb, MSD, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi
Consulting or Advisory Role: Roche, Bristol-Myers Squibb, MSD, Novartis, Amgen, Takeda, Pierre Fabre, Sun Pharma, Sanofi
Research Funding: Roche (Inst), Bristol-Myers Squibb (Inst), Novartis (Inst), MSD (Inst), Amgen (Inst)

Dirk Schadendorf
Honoraria: Roche/Genentech, Novartis, Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Sysmex, Immunocore, Grünenthal Group, Merck Serono, Agenus, Array BioPharma, AstraZeneca, LEO Pharma, Incyte, Pfizer, Pierre Fabre, Philogen, Regeneron, 4SC, Mologen
Consulting or Advisory Role: Roche/Genentech, Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, Merck Serono, Amgen, Immunocore, Incyte, 4SC, Pierre Fabre, Mologen, Sanofi/Regeneron
Speakers' Bureau: Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Amgen, Incyte, Pierre Fabre
Research Funding: Bristol-Myers Squibb (Inst), Novartis (Inst)
Travel, Accommodations, Expenses: Roche/Genentech, Bristol-Myers Squibb, Amgen, Merck, Merck Serono, Novartis

Victoria Atkinson
Honoraria: Bristol-Myers Squibb, Novartis, Merck Sharp & Dohme, Pierre Fabre
Consulting or Advisory Role: Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Merck Serono, Pierre Fabre, Roche
Speakers' Bureau: Roche/Genentech, Bristol-Myers Squibb, Novartis, Merck Sharp & Dohme, Merck Serono
Travel, Accommodations, Expenses: Bristol-Myers Squibb, OncoSec

Mario Mandalà
Honoraria: MSD Oncology, Novartis, Roche/Genentech, Bristol-Myers Squibb, Pierre Fabre
Consulting or Advisory Role: Novartis, Bristol-Myers Squibb, Pierre Fabre, Roche/Genentech, MSD Oncology
Research Funding: Novartis (Inst), Roche/Genentech (Inst)

Vanna Chiarion-Sileni
Consulting or Advisory Role: MSD Oncology, Merck Serono, Bristol-Myers Squibb, Novartis, Pierre Fabre, Roche
Speakers' Bureau: Bristol-Myers Squibb, Novartis
Travel, Accommodations, Expenses: Bristol-Myers Squibb

James Larkin
Honoraria: Eisai, Bristol-Myers Squibb, MSD, GlaxoSmithKline, Pfizer, Novartis, Roche/Genentech, Pierre Fabre, EUSA Pharma, Secarna, Achilles Therapeutics, AstraZeneca, Boston Biomedical, Ipsen, Imugene, Incyte, iOnctura, Kymab, Merck Serono, Nektar, Vitaccess
Consulting or Advisory Role: Eisai, Bristol-Myers Squibb, MSD, GlaxoSmithKline, Pfizer, Novartis, Roche/Genentech, Pierre Fabre, EUSA Pharma, Sectra, Achilles Therapeutics, AstraZeneca, Boston Biomedical, Ipsen, Imugene, Incyte, iOnctura, Kyocera, Merck Serono, Nektar, Vitaccess
Research Funding: Pfizer (Inst), Novartis (Inst), MSD (Inst), Bristol-Myers Squibb (Inst), Achilles Therapeutics (Inst), Roche (Inst), Nektar (Inst), Covance (Inst), Immunocore (Inst), AVEO (Inst)
Travel, Accommodations, Expenses: Bristol-Myers Squibb, Pfizer, Novartis, Roche/Genentech

Marta Nyakas
Consulting or Advisory Role: Novartis (Inst), Incyte (Inst), MSD Oncology (Inst)

Caroline Dutriaux
Consulting or Advisory Role: Bristol-Myers Squibb, MSD, Novartis, Roche

Andrew Haydon
Honoraria: Novartis, Merck
Consulting or Advisory Role: Novartis, Pierre Fabre
Speakers' Bureau: Novartis, Merck

Caroline Robert
Consulting or Advisory Role: Bristol-Myers Squibb, Roche, Merck, Novartis, Pierre Fabre, Merck Serono, MSD, Array, Sanofi

Laurent Mortier
Travel, Accommodations, Expenses: Roche/Genentech, Novartis, Bristol-Myers Squibb

Jacob Schachter
Honoraria: Bristol-Myers Squibb, MSD
Consulting or Advisory Role: MSD, Bristol-Myers Squibb
Travel, Accommodations, Expenses: Bristol-Myers Squibb

Thierry Lesimple
Consulting or Advisory Role: Roche, Novartis, MSD, Incyte
Speakers' Bureau: MSD, Bristol-Myers Squibb, Roche, Novartis
Research Funding: Roche (Inst)
Travel, Accommodations, Expenses: Roche, MSD

Ruth Plummer
Honoraria: Roche/Genentech, Bristol-Myers Squibb, Pfizer (I)
Consulting or Advisory Role: Roche/Genentech, Clovis Oncology, MSD Oncology, Novartis, Astex Pharmaceuticals, Pierre Fabre, Bayer, Octimet, Biosceptre, Ellipses Pharma, Karus Therapeutics
Speakers' Bureau: Novartis
Research Funding: AstraZeneca (Inst), MedImmune (Inst)
Patents, Royalties, Other Intellectual Property: Named on patent for use of PARP inhibitor rucaparib (Inst)
Travel, Accommodations, Expenses: MSD Oncology, Bristol-Myers Squibb

Kohinoor Dasgupta
Employment: Novartis

Tomas Haas
Employment: Novartis
Stock and Other Ownership Interests: Novartis
Travel, Accommodations, Expenses: Novartis

Mark Shilkrut
Employment: Novartis
Stock and Other Ownership Interests: Novartis

Eduard Gasal
Employment: Novartis
Stock and Other Ownership Interests: Novartis

Richard Kefford
Consulting or Advisory Role: Amgen (Inst), Teva Pharmaceuticals (Inst)
Travel, Accommodations, Expenses: Bristol-Myers Squibb, Amgen

John M. Kirkwood
Consulting or Advisory Role: Bristol-Myers Squibb, Novartis, Array BioPharma, Roche, Immunocore
Research Funding: Merck (Inst), Prometheus Laboratories (Inst), Immunocore (Inst)

Axel Hauschild
Honoraria: Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Roche, Provectus, Pierre Fabre, Regeneron
Consulting or Advisory Role: Amgen, Bristol-Myers Squibb, MedImmune, Merck Serono, Merck Sharp & Dohme, Novartis, OncoSec, Roche, Nektar, Philogen, Provectus, Regeneron Sanofi-Genzyme, Sun Pharma
Research Funding: Amgen (Inst), Bristol-Myers Squibb (Inst), GlaxoSmithKline (Inst), Merck Serono (Inst), Merck Sharp & Dohme (Inst), Novartis (Inst), Philogen (Inst), Pierre Fabre (Inst), Provectus (Inst), Regeneron (Inst), Roche (Inst)

No other potential conflicts of interest were reported.